

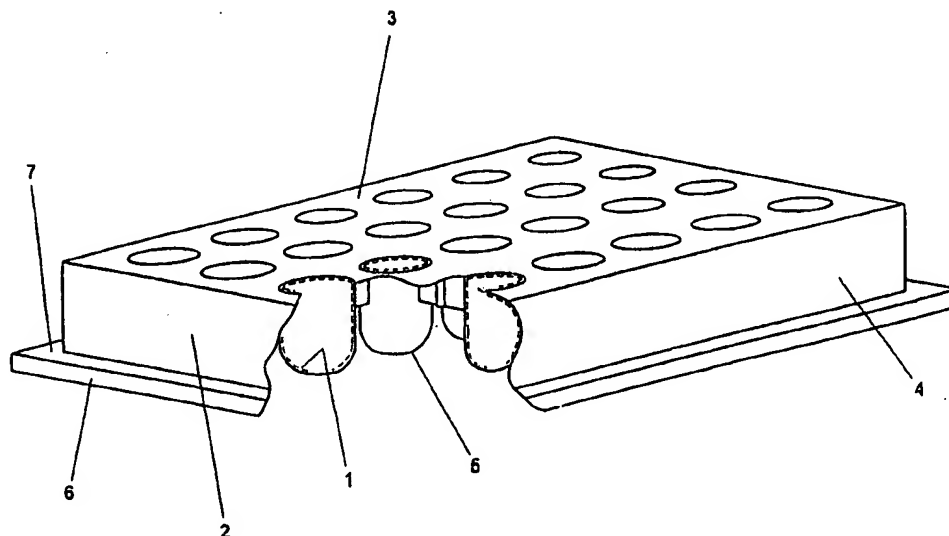
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(21) International Application Number: PCT/NL98/00711 (22) International Filing Date: 11 December 1998 (11.12.98) (30) Priority Data: 1007781 12 December 1997 (12.12.97) NL (71) Applicant (for all designated States except US): PACKARD BIOSCIENCE B.V. [NL/NL]; Ulgersmaweg 47, NL-9731 BK Groningen (NL). (72) Inventors; and (75) Inventors/Applicants (for US only): THOMSON, James [GB/US]; 110 Steeplechase Drive, Newington, CT 06111 (US). TER WIEL, Jan [NL/NL]; Molenweg 47, NL-9919 AG Loppersum (NL). (74) Agent: OTTEVANGERS, S., U.; Verenigde Octrooibureaux, Nieuwe Parklaan 97, NL-2587 BN The Hague (NL).		(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.

(54) Title: MICROTITER PLATE WITH COATING



(57) Abstract

The invention relates to a plastic microtiter plate provided with a coating which comprises a para-xylylene polymer, and to a method for applying such a coating to a plastic microtiter plate. The invention also relates to the use of such a microtiter plate in carrying out chemical, biochemical, biological, clinical or pharmaceutical analyses.

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Title: MICROTITER PLATE WITH COATING

This invention relates to a microtiter plate and to a method for applying a coating thereto.

Microtiter plates have long been widely used aids in a laboratory. They are part of the standard equipment in laboratories where analyses are carried out. There are numerous examples of such analyses in the world of pharmaceutical, biological and clinicomedical research.

The wells, or receiving cavities, of a microtiter plate lend themselves eminently for carrying out different chemical and/or biochemical reactions on a small scale. In practice, microtiter plates are often used for carrying out chemical, biochemical and/or enzymatic reactions. In carrying out immunoassays, too, whether or not using radioactive labels, microtiter plates are frequently used. They are useful especially for carrying out various test reactions for the quantitation of substances to be analyzed. Such test reactions may be, for instance, luminescence or fluorescence reactions, or assays of radioactivity using scintillation counting (LSC).

Because of the application of the microtiter plate in a very wide range of reactions, the material of which it is made should be chemically resistant and inert to a sufficient extent. For that reason, the first microtiter plates were made of ceramic materials, such as porcelain or glass, which are still eminently satisfactory in many cases.

At present, however, it is desired to carry out many analyses and reactions on a smallest possible scale. Although, indeed, microtiter plates as such are eminently suitable for this purpose, it has been found difficult to form ceramic microtiter plates whose wells are small enough. In other words, ceramic materials are less suitable for making microtiter plates on which analyses or reactions are to be performed where the volume of test or reaction mixture is very small.

An example of a field where it is desired to perform reactions on a very small scale is the so-called combinatorial chemistry. This technique currently enjoys much interest, in particular on the part of the pharmaceutical industry. In this technique, a large number of substances are synthesized in an automated manner. The thus obtained substances can subsequently be tested for certain properties (in an automated manner). This is called 'high throughput screening'.

To carry out such a large number of chemical reactions economically, the amounts of starting materials to be used should be as small as possible. To that end, as stated, use is made of microtiter plates having wells of very small dimensions, which wells are regularly shaped and are regularly spaced apart. For this purpose, microtiter plates are manufactured which have 384 wells to 1536 wells. A microtiter plate having a great multiplicity of wells is sometimes referred to as nanoplate, since in such a case the volume of a single well is only a few nanoliters. It has been found that forming such microtiter plates from porcelain is extremely difficult. By way of alternative, often a polymeric material is used for manufacturing these microtiter plates.

It has been found, however, that it is not easy to find a polymeric material that is suitable for making a microtiter plate. The fact is that the material of a microtiter plate must satisfy high standards. The material must have the desired reflective properties - or it must be readily possible to impart these properties to the material, for instance by addition of a color - so that the microtiter plate can be used in LSC and fluorescence or luminescence measurements. The material must have such mechanical properties as to enable both easy handling (stiffness) and ready and accurately reproducible manufacture. Further, the material, while maintaining mechanical properties, should be resistant to the influence

of both increased and lowered temperatures, since the conditions under which it must be possible to use the microtiter plates vary widely. Also, the material, as already noted hereinabove in more general terms, must be resistant to the influence of various chemical compounds and solvents.

The requirements of stiffness and reflective properties can be met by many polymeric materials. Also, microtiter plates can be manufactured simply and accurately in the desired form. It is difficult, however, to find a polymeric material that not only has the required mechanical properties but also has sufficient resistance to low and high temperatures and sufficient chemical resistance and inertness. Although the ceramic materials used heretofore are sufficiently resistant to influences of temperature and chemicals, ceramic material, as stated, is less suitable for manufacturing microtiter plates therefrom in a simple and reproducibly accurate manner.

U.S. Patent 5,544,218 discloses an alternative to a microtiter plate. The document pertains to the problems that present themselves in handling very small samples for irradiation experiments. Because of the small amounts that are used as sample in such experiments, the exact position where the sample is provided is often difficult to define precisely, which may disturb the results of an irradiation experiment. It is proposed to solve this problem by providing a sample on a thin, elastic polymer film which is supported by a holder and in which wells are provided. The holder is provided with one or more orifices, over which the polymer film is fixed. By stretching the polymer film to some extent at the positions of the orifices of the support, the polymer film starts to sag, as it were, thereby forming a well. The polymer film may be made of different materials, such as polyimide, polyvinyl formal, polycarbonate, polypropylene and the like.

It is an object of the invention to provide a microtiter plate of materials whereby the favorable properties of a ceramic and a polymeric material are combined. According to the invention, a microtiter plate is contemplated which is at least as inert and chemically resistant as a ceramic microtiter plate, but which is made of a material from which nanoplates can be manufactured in an accurate manner.

It has presently been found, surprisingly, that this object can be achieved by applying a specific coating to a plastic microtiter plate. Accordingly, this invention relates to a plastic microtiter plate provided with a coating which comprises a para-xylylene polymer.

It has been found that by the presence of a coating of a para-xylylene polymer, a great many materials as such not suitable, or less suitable, for making microtiter plates, can yet be utilized for this purpose. Microtiter plates according to the invention satisfy the above-mentioned requirements, that is, the material is suitable for making therefrom microtiter plates having wells of a volume of from a few nanoliters to a few milliliters, while further being eminently chemically resistant and inert and having good reflective properties.

Measurements which, as part of a particular analysis, are performed on substances in wells of a microtiter plate according to the invention, are not adversely affected by the presence of the coating. By virtue of the coating, the chemical resistance of the microtiter plate is so high that the material of which the microtiter plate is made does not disturb the measurements unacceptably.

According to the invention, a microtiter plate is understood to mean a support, which support is provided with a matrix of receiving cavities or wells. Fig. 1 shows an example of a microtiter plate. Both the support and the receiving cavities may vary in dimensions. Conventional

dimensions vary from about 10-15 x 6-9 cm. A widely used standard dimension is 127.85 x 85.65 mm. Depending on the desired application of the microtiter plate, dimensions may deviate from those mentioned. The thickness of a microtiter plate is not critical. The number of receiving cavities will depend on the desired magnitude of the volume. Conventional numbers range from 12 to 3456 and, for practical purposes, are mostly multiples of four. By way of illustration, it may be mentioned that the wells of a plate having 24 wells each have a volume of 1.5 ml, while the wells of an equally large plate having 1536 wells each have a volume of a few nanoliters.

Suitable materials of which a microtiter plate according to the invention may be made are all plastics having such properties that a microtiter plate having the desired number of regularly shaped wells can be manufactured. Further, the plastic should be sufficiently stiff, so that the microtiter plate can be readily handled.

Both homopolymers and copolymers can be used. Suitable examples comprise vinyl polymers, such as styrene polymers and copolymers of styrene, polyvinyl chloride or polymethyl methacrylate, polyethylene terephthalate, polycarbonates, polyaryl ethers, polyether esters, polyether ketones, polyetherester ketones, polyurethanes, and mixtures thereof. Preferred are polystyrene, polyacrylates, polyvinyl chloride, polyamides and Barex® (a polyacrylonitrile copolymer).

Particularly preferred is polystyrene. It has been found that microtiter plates of polystyrene combine the properties already mentioned, such as thermal stability, stiffness and dimensional reproducibility, with good miscibility with colors, such as titanium oxide, to obtain desired reflective properties. Moreover, the use of polystyrene is also appealing from the point of view of economy.

According to the invention, the coating should in any case be applied to the surface in the wells 1 (see Fig. 1). It is preferred that the coating is further present on the entire side where the openings of the receiving cavities are located, i.e. the upper side 3. Under certain circumstances, it may additionally be desirable that the coating is further applied to the sides of the plate 2, 4, 6, 7. This is especially advantageous when there is a good chance that in the use of the microtiter plate, chemicals leak onto the plate. It is particularly preferred that all surfaces of the microtiter plate, that is, all surfaces already mentioned plus the underside 5, are coated with a coating layer according to the invention.

The coating, which, according to the invention, is applied to a microtiter plate, comprises a para-xylylene polymer, such as Parylene[®]. Surprisingly, a microtiter plate on which a coating comprising a para-xylylene polymer has been applied, has been found to exhibit exceedingly good chemical resistance and inertness. This makes it possible to expose the microtiter plate to a large variety of chemicals and solvents. It has further been found that the above-mentioned desired properties of the plastic, of which a microtiter plate according to the invention is made, have been maintained. Optionally, the properties of a microtiter plate can be optimized by providing particular functional groups, as desired, on the surface of the coating comprising a para-xylylene polymer.

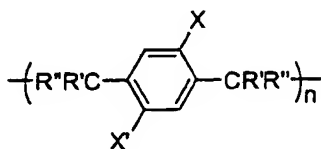
The coating can be applied, as desired, in varying thicknesses, ranging from 0.1 to more than 50 μm . Further, the coating can very simply be applied uniformly over the microtiter plate. This holds especially when the coating is based on a para-xylylene polymer, which is a preferred embodiment of the invention. Even in the case of very thin coating layers, the coating is pin-hole free, so that there is no risk of crack formation in the coating, and complex

geometric shapes can be coated. An additional advantage is that a coating comprising a para-xylylene polymer is sufficiently transparent, so that the reflective properties of the plastic of which the microtiter plate according to the invention is made are retained.

It is noted that the application of parylene coatings is known per se. In microelectronics and the aircraft industry, the material is used because of its low water permeability. Moisture- and water-sensitive microelectronic equipment can be protected with a parylene coating film. U.S. Patent 4,225,647 discloses the use of para-xylylene polymers for applying a protective film to various objects, such as art objects, coins, car parts, fishing gear, and the like. This typically involves the protection of surfaces that are subject to corrosion or mechanical wear. Further, it is known from U.S. Patent 5,380,320 to coat articles used for medical purposes, such as catheters and cannulae, with parylene. The reason is that the material, in addition to being electrically insulating, has eminent biocompatibility.

Because of that biocompatibility of para-xylylene polymers, a microtiter plate according to the invention can be used in applications where living cells play a role, as in so-called homogeneous bioassays. It has been found that in such an application, no disadvantageous binding of cells to the microtiter plate according to the invention occurs. This is sometimes referred to, in this connection, as cellular, non-adhesive functionality. If desired, this functionality can be reversed by cold surface plasma modification, which enables a choice between the desired properties, cellular adhesion or cellular non-adhesion. In a comparable manner, the possibility for a microtiter plate according to the invention to bind other biomolecules, such as proteins, can be controlled.

Para-xylylene polymers that are particularly suitable for the use according to the invention are polymers satisfying the formula (I):



(I),

wherein

R', R'', X and X' independently represent a hydrogen atom or a halogen atom. It is preferred for a coating on a microtiter plate according to the invention to comprise parylene C®, parylene N®, parylene D® or parylene AF-4®. Parylene C is a polymer of the formula (I), wherein X', R' and R'' are all hydrogen and X represents a chlorine atom. Parylene N is a polymer of the formula (I), wherein X, X', R' and R'' are all hydrogen. Parylene D is a polymer wherein R' and R'' are both hydrogen and X and X' both represent a chlorine atom. Parylene AF-4 is a polymer wherein X and X' both represent a hydrogen atom and R' and R'' both represent a fluorine atom.

This invention further relates to a method for applying a coating which comprises a para-xylylene polymer to a microtiter plate. According to the invention, a coating is applied utilizing a gas phase deposition process. Such a process is known from U.S. Patents 3,288,728 and 3,342,754 and has as advantages that a uniform coating film of uniform thickness is realized and that the use of a solvent is avoided. It is possible, using this method, to coat surfaces not accessible for a coating applied in the liquid phase, without the various surfaces being connected to each other. This last is meant to say that it is undesired that the wells of the microtiter plate are wholly or partly filled up by the application of a coating.

According to the invention, the first step for applying a coating to a microtiter plate comprises bringing

a para-xylylene dimer into the gas phase. The nature of the para-xylylene dimer is selected on the basis of the nature of the eventual para-xylylene polymer. The selected dimer is heated to about 120-180°C, preferably 140-160°C, at a pressure of 75 to 200 Pa, preferably 100-150 Pa.

In the second step, the product obtained in the first step is pyrolyzed. This can be done in a suitable manner at a temperature of between 600 and 750°C, preferably between 650 and 700°C, and a pressure of 30 to 100 Pa, preferably 50-75 Pa. After this step, para-xylylene in monomeric form is obtained.

The third step comprises the actual deposition of the para-xylylene polymer on the microtiter plate. This deposition is carried out at a temperature of 20-50°C, preferably 25-40°C, and a pressure of 5-20 Pa, preferably 10-15 Pa. The thickness of the coating film to be deposited can be controlled by selecting a suitable residence time of the microtiter plate in the deposition chamber, i.e., the space in which the deposition is carried out. Given a particular desired thickness, those skilled in the art will be able to determine a suitable residence time on the basis of their knowledge.

It is preferred that the three steps for applying a coating comprising a para-xylylene polymer is carried out in three different reaction chambers.

Finally, this invention further relates to the use of a microtiter plate which has been provided with a coating in the above-described manner, in carrying out chemical, biochemical, biological, clinical or pharmaceutical analyses. In particular, the invention relates to the use of the microtiter plate in carrying out test reactions, such as luminescence or fluorescence reactions, or in assays of radioactivity, for instance using scintillation counting (LSC).

The invention will presently be further explained in and by the following examples.

EXAMPLESIntroduction:

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When a microtiter plate of polystyrene, in which titanium dioxide has been incorporated as whitener, is filled with a cocktail for liquid scintillation counting experiments, there will occur, depending on the solvent of the cocktail, a slow but progressive process whereby the polystyrene of the plate is affected and becomes weak. Simultaneously, a certain amount of the whitener migrates from the wall to the cocktail, so that the results of the experiments will be adversely affected. Also, as a result, the reflective properties of the microtiter plate will be wholly or partly lost.

By adding radioactive material, for instance tritiated hexadecane, to the cocktail, it can be quantitated on a TopCount. This is an instrument capable of measuring luminescence and radioactivity in the form of a light in microtiter plates. When the surface of the plate is affected, fewer counts (cpm) are registered over time.

Example I: Coating a microtiter plate

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Six grams of the cyclic dimer [2.2]-paracyclophane were heated to 140°C and then sublimed under a pressure of 10 µm Hg. The sublimed vapors were passed into an oven, which was held at a temperature of 680°C and a pressure of 10 µm Hg. In the oven, the dimer was converted into reactive diradicals. These diradicals were passed into a deposition zone, where an OPTIPLATE with 96 wells (Packard Instrument, Downers Grove, Ill., USA) was disposed. As soon as the radicals contacted the OPTIPLATE, a thin hard coating layer of poly(para-xylylene) deposited on all surfaces of the OPTIPLATE. The residual vapors which did

not condense in the deposition zone were removed via a cold trap with a vacuum pump.

Example II: Comparison of the influence of a
5 scintillation liquid on the light yield in a microtiter plate with a parylene coating and without parylene coating.

A. In 12 wells of a microtiter plate according to Example I, 200 µl Microscint O (Packard Instrument, Downers
10 Grove, Ill., USA) was provided. Then, in 6 of these wells, 40 µl (20% v/v) xylene was added. After that, 10 µl tritiated hexadecane (Packard Instrument, Downers Grove, Ill., USA) was added to the wells, followed by shaking for 5 minutes on an orbital shaker to obtain homogeneous
15 mixtures. After the microtiter plate was taped up with TopSeal A (Packard Instrument, Downers Grove, Ill., USA), it was counted in a Top Count microplate scintillation counter. At set times (see Table A), the plate was measured.

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B. The above procedure was repeated with a microtiter plate (OPTIPLATE with 96 wells, Packard Instrument, Downers Grove, Ill., USA) which is not provided with a coating (see Table B).

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In the counting of the two plates, the following settings were used:

30	- temperature:	19°C
	- count delay:	5 minutes
	- count time:	3 minutes
	- data mode:	Liquid low high
	- region A:	2.9-35
	- data:	cpm

Table A:

Date	Time	Microscint O, cpm	Microscint O and 20% xylene, cpm
12/5/1997	13:53	10316	8082
13/5/1997	11:38	10405	8395
14/5/1997	12:15	10375	8407

5

Table B:

Date	Time	Microscint O, cpm	Microscint O and 20% xylene, cpm
12/5/1997	11:10	10209	8216
13/5/1997	8:55	9673	7260
14/5/1997	9:32	8532	6637

10 It appears from Tables A and B that the cpm values in the plate with a coating according to the invention remain constant. The cpm values in the plate on which no coating is provided show a decrease. This shows that plate material (polystyrene) and whitener have dissolved in the mixture in the wells.

CLAIMS

1. A plastic microtiter plate provided with a coating which comprises a para-xylylene polymer.
2. A microtiter plate according to claim 1, wherein the para-xylylene polymer is selected from the group consisting of parylene C, parylene N, parylene D and parylene AF-4.
3. A microtiter plate according to claim 1 of 2, wherein the coating has a thickness of between 0.1 and 50 μm .
4. A microtiter plate according to claims 1-3, which microtiter plate is a microtiter plate or a nanoplate.
5. A microtiter plate according to claims 1-4, wherein the microtiter plate is manufactured from polystyrene, polyvinyl chloride or polyacrylonitrile.
6. A method for applying a coating which comprises a para-xylylene polymer to a microtiter plate, wherein a para-xylylene dimer is brought into the vapor phase, is pyrolyzed and is deposited on the microtiter plate.
7. A method according to claim 6, wherein the para-xylylene dimer is brought into the vapor phase by heating to about 120-180°C, preferably 140-160°C, at a pressure of 75 to 200 Pa, preferably 100-150 Pa.
8. A method according to claim 6 or 7, wherein pyrolyzing is carried out at a temperature of between 600 and 750°C, preferably between 650 and 700°C, and a pressure of from 30 to 100 Pa, preferably 50-75 Pa.
9. A method according to claims 6-8, wherein the deposition is carried out at a temperature of 20-50°C, preferably 25-40°C, and a pressure of 5-20 Pa, preferably 10-15 Pa.
10. A method according to claims 6-9, wherein the microtiter plate is made of polystyrene, polyvinyl chloride or polyacrylonitrile.

11. Use of a para-xylylene polymer for coating a microtiter plate for improving the chemical resistance of said microtiter plate..
12. Use of a microtiter plate according to claims 1-5 in
5 carrying out chemical, biochemical, biological, clinical or pharmaceutical analyses.
13. Use of a microtiter plate according to claim 12 in carrying out test reactions, such as luminescence or fluorescence reactions, or in assays of radioactivity, for
10 instance using scintillation counting (LSC).

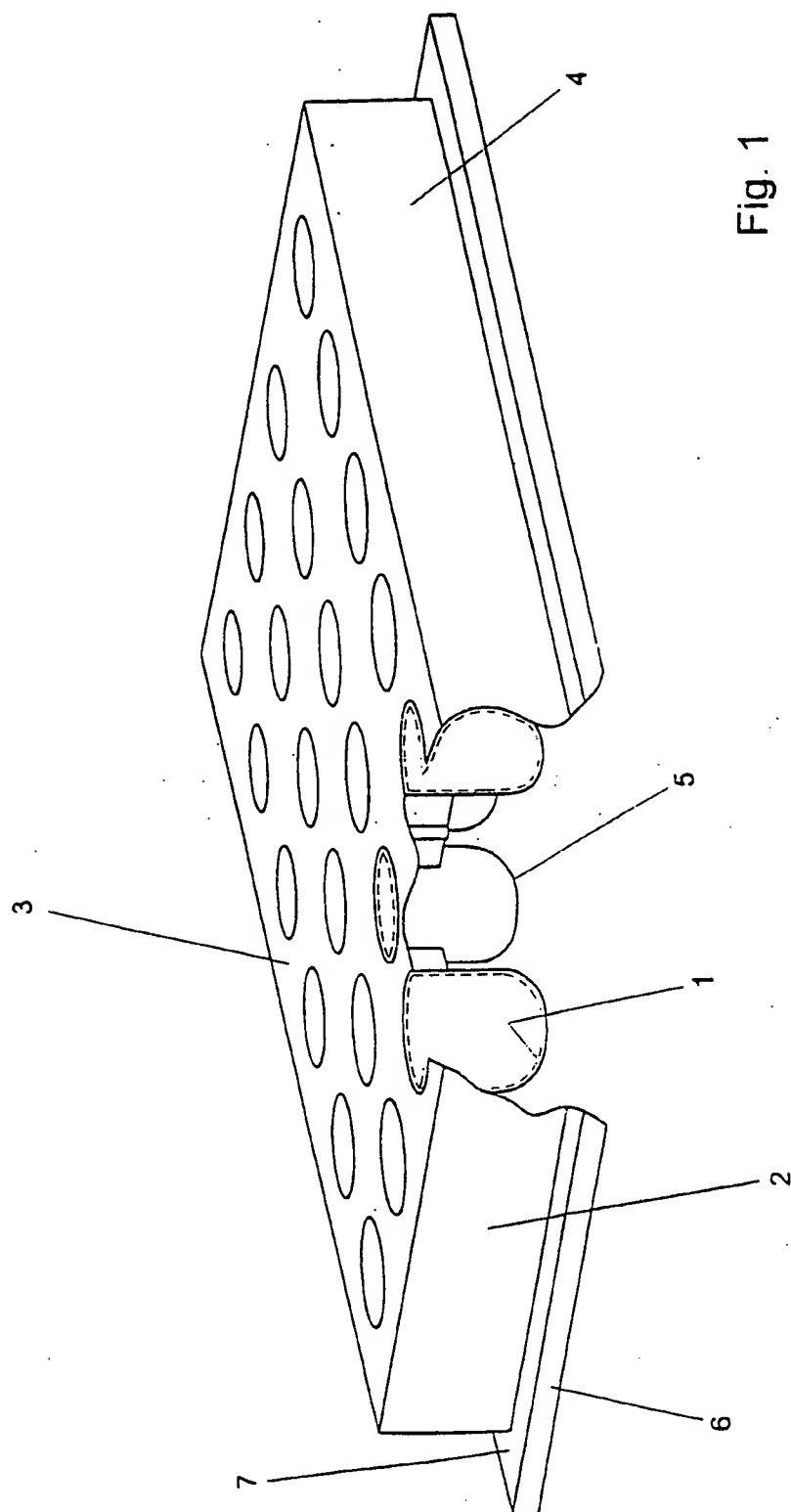


Fig. 1

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01L3/00 G01N35/02 //B05D7/24,B05D3/14,C08F2/00,C08J7/04

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Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01L G01N B05D C08F C08J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

19/03/1999

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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